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Year: 2013

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## **Vestibular impairment in patients with Charcot-Marie-Tooth disease**

Poretti, A ; Palla, A ; Tarnutzer, A A ; Petersen, J A ; Weber, K P ; Straumann, D ; Jung, H H

**Abstract:** **OBJECTIVE:** This case-control study aimed to determine whether the imbalance in Charcot-Marie-tooth (CMT) disease is caused only by reduced proprioceptive input or whether the involvement of the vestibular nerve is an additional factor. **METHODS:** Fifteen patients with CMT disease (aged  $48 \pm 17$  years; 8 women) underwent cervical vestibular-evoked myogenic potentials, which reflect otolith-spinal reflex function, and quantitative horizontal search-coil head-impulse testing, which assesses the high-acceleration vestibulo-ocular reflex of the semicircular canals. **RESULTS:** Relative to healthy age-matched control subjects, cervical vestibular-evoked myogenic potentials were found to be impaired in 75% of patients (average p13 latency:  $23.0 \pm 2.7$  milliseconds,  $p = 0.01$ ; average n23 latency:  $29.0 \pm 1.8$  milliseconds,  $p = 0.01$ ) and the quantitative head-impulse test in 60% of patients (average gain  $\pm 1$  SD:  $0.67 \pm 0.24$ ,  $p < 0.001$ ). All patients with head-impulse test impairment also showed cervical vestibular-evoked myogenic potential abnormalities, while the reverse was not true. **CONCLUSIONS:** We conclude that the neuropathic process in patients with CMT disease frequently involves the vestibular nerve and that cervical vestibular-evoked myogenic potentials may be more sensitive than quantitative head-impulse testing for detecting vestibular involvement, in particular at an early disease stage.

DOI: <https://doi.org/10.1212/WNL.0b013e318295d72a>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-84931>

Journal Article

Accepted Version

Originally published at:

Poretti, A; Palla, A; Tarnutzer, A A; Petersen, J A; Weber, K P; Straumann, D; Jung, H H (2013). Vestibular impairment in patients with Charcot-Marie-Tooth disease. *Neurology*, 80(23):2099-105.

DOI: <https://doi.org/10.1212/WNL.0b013e318295d72a>

## **Vestibular impairment in patients with Charcot-Marie-Tooth disease**

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word count for the text: 3131  
word count for the abstract: 182  
character count for the title: 65  
number of figures: 3  
number of tables: 1

Running title: Vestibular function in Charcot-Marie-Tooth disease

Key words: head impulse test; vestibular evoked myogenic potentials; polyneuropathy; neuro-otology

Authors' contributions: A. Palla, A. Poretti, D. Straumann, and H. H. Jung

conceptualized and designed the study; A. Palla and A. Poretti analyzed and interpreted and drafted the manuscript; D. Straumann, K. P. Weber and A. A. Tarnutzer critically revised the manuscript for intellectual content; all authors participated in the acquisition of data and read and approved the final manuscript.

Statistical analysis: Statistical analysis was conducted by A. Palla and A. Poretti

Disclosure: Authors A. Pa., A. Po. A. A. T., J. A. P., D. S., and H. H. J do not report conflict of interest. Author K. P. W. acts as an unpaid consultant and has received funding for travel from GN Otometrics

Grant / financial support: Swiss National Science Foundation; Betty and David Koetser Foundation for Brain Research; Baasch Medicus Foundation; Zurich Center for Integrative Human Physiology

Acknowledgments: The authors thank Dr. S.M. Rosengren for valuable comments and E. Buffone and M. Penner for technical assistance.

## ABSTRACT

**Objective:** This case-control study aimed to determine whether the imbalance in Charcot-Marie-Tooth (CMT) disease is caused only by reduced proprioceptive input or whether the involvement of the vestibular nerve is an additional factor.

**Methods:** 15 CMT patients ( $48 \pm 17$  y; 8 women) underwent cervical vestibular-evoked myogenic potentials, which reflect otolith-spinal reflex function, and quantitative horizontal search-coil head-impulse testing, which assesses the high-acceleration vestibulo-ocular reflex of the semicircular canals.

**Results:** Relative to healthy age-matched control subjects, cervical vestibular-evoked myogenic potentials were found to be impaired in 75% (average p13 latency:  $23.0 \pm 2.7$  ms;  $p = 0.01$ ; average n23 latency:  $29.0 \pm 1.8$  ms;  $p = 0.01$ ) and the quantitative head-impulse test in 60% (average gain  $\pm 1$ SD:  $0.67 \pm 0.24$ ;  $p < 0.001$ ) of patients. All patients with head-impulse test impairment also showed cervical vestibular-evoked myogenic potential abnormalities, while the reverse was not true.

**Conclusions:** We conclude that the neuropathic process in CMT patients frequently involves the vestibular nerve and that cervical vestibular-evoked myogenic potentials may be more sensitive than quantitative head-impulse testing for detecting vestibular involvement, in particular at an early disease stage.

## INTRODUCTION

In patients with Charcot-Marie-Tooth disease (CMT) it is generally assumed that proprioceptive sensory loss causes sensory ataxia leading to postural instability. However, vestibular impairment could also contribute to the imbalance. In fact, involvement of the vestibular nerve in the polyneuropathic process has been shown to occur frequently in patients with non-inherited polyneuropathy <sup>1-4</sup> and interestingly, sensory neuropathy seems to be an integral part of the just recently characterized syndrome of cerebellar ataxia with bilateral vestibulopathy. <sup>5</sup> In inherited neuropathy, vestibular hypofunction has been, so far, documented only in single case reports, including the description of bilateral vestibular loss in two patients with Dejerine–Sottas syndrome <sup>6</sup> and of vestibular neuropathy in a Roma family with hereditary motor and sensory peripheral neuropathy due to mutations on chromosome 8p24. <sup>7</sup> Given the evidence that vestibular rehabilitation improves postural stability in patients with vestibulopathy, <sup>8</sup> identifying a concomitant vestibular impairment is clinically important.

In the current study, we set out to determine the frequency of vestibular impairment in patients with CMT. By assessing vestibular semicircular canal and otolith function we further aimed to detect specific patterns of vestibular deficits.

## MATERIAL AND METHODS

**Standard protocol approvals and patient consents.** Informed consent was obtained from all participants after a full explanation of the experimental procedure. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects.

**Study cohort and eligibility criteria.** Participants of this case-control study were selected for eligibility from patients referred to our tertiary neurologic center for further evaluation of neuropathic symptoms between March 2009 to March 2010. Inclusion criteria were: clinically affected status defined as muscle weakness of at least the foot dorsiflexors. Exclusion criteria were other known disease or medication that may cause neuropathy, reluctance to undergo nerve conduction studies, low CMAP amplitude of the abductor pollicis brevis muscle (negative peak < 0.5 mV) hindering proper determination of the motor nerve conduction velocity (MNCV) of the median nerve.

**Procedure.** Detailed history taking and complete neurologic examination were performed. Patients were specifically assessed for spontaneous and gaze-evoked nystagmus, correcting saccades following Halmagyi-Curthoys head impulses,<sup>9</sup> positional and positioning nystagmus, muscle atrophy, weakness, weak or absent tendon reflex, as well as stand, gait, and limb ataxia. Sensory examinations included touch, pain, temperature, vibration, and position sense. Vibration sense was tested with a 128 Hz tuning fork at the ankles, knees, and index fingers and considered reduced at 4/8 or below.<sup>10</sup> All patients were examined by one of four authors (A. Po., A. Pa., H. H. J., J. A. P.). Data about the genotype were collected in all but one patient (Patient ID 15), in whom family history was positive for Charcot-Marie-Tooth Type 1A.

All patients underwent electrophysiological investigations. Investigations were performed by one of two authors (A. A. T, J. A. P.) and supervised by two senior authors (K. P. W, H. H. J.). Standard nerve conduction studies (motor and sensory) included the median, ulnar, and peroneal nerves on one side (if the severity of the neurological impairments was asymmetric, the investigation was performed on the more affected side). Age-related normative values were taken from Ludin.<sup>11</sup> Charcot-Marie-Tooth (CMT) neuropathies were subdivided in 1) a predominant demyelinating form characterized by nerve-conduction velocities < 38 m/s in upper-limb motor nerves and 2) a primary axonal form with nerve-conduction velocities > 38 m/s in upper-limb motor nerves (subdivision according to<sup>12-14</sup>).

Vestibular function was characterized by cervical vestibular-evoked myogenic potentials (cVEMP) for otolith function assessment and the quantitative head impulse test (qHIT) for semicircular canal function assessment. cVEMP were registered from contracted sternocleidomastoid muscles (SCM). Air-conducted sound stimuli for cVEMP (500-Hz, 6 ms-tone bursts at 90-100 dB normal hearing level [nHL], total of 200 bursts) were presented through calibrated headphones (Telephonics TDH39P) monaurally to the right and left ears. During stimulation, subjects were asked to sit and turn their head as much as possible to the side to tense their SCM. Electromyographic (EMG) activity was recorded (Viking V system, Nicolet Biomedical USA) from the upper half of the SCM muscle with a reference electrode on the upper sternum. The background SCM contraction was monitored online and measured over the 20 ms pre-stimulus interval (using root mean square EMG). Signals of 200 air-conducted cVEMP stimuli were averaged. The resultant response consisted of an initial positive peak (p13) and a subsequent negative peak (n23). p13-n23 amplitudes, p13-, and n23-latencies were calculated for each ear. Because of the large inter-individual variability in cVEMP

amplitudes (ranging from 2 to 181  $\mu$ V), side to side differences in uncorrected reflex amplitudes were expressed as asymmetry ratio (AR) calculated as <sup>15</sup>:

$$AR = \frac{(A_l - A_s)}{(A_l + A_s)} * 100$$

where  $A_l$  is the larger and  $A_s$  is the smaller amplitude obtained from stimulating each ear. <sup>16</sup> Subjects with bilaterally absent responses were not included in the calculation of asymmetry ratio. The upper normal limit of asymmetry ratio was set to 46 % (value for uncorrected background EMG) as suggested by Wegampola and Colebatch. <sup>16</sup> 18 age-matched healthy subjects ( $45 \pm 15$  y, range 25 - 67 y) served as controls. The average asymmetry ratio value in our healthy control group ( $26 \pm 15$  %; range 5 – 60 %) was comparable to Wegampola and Colebatch (23 %). <sup>16</sup> p13- and n23-latency values were  $15.5 \pm 1.9$  ms and  $25.5 \pm 1.3$  ms (average  $\pm$  1 standard deviation), respectively. Average  $\pm$  2 standard deviations were defined as the upper limit of the normal range, that is p13 = 19.3 ms and n23 = 28.1 ms.

For qHIT, eye and head movements were recorded in a magnetic frame (Remmel type system, modified by A. Lasker, Baltimore, MA) using search-coils, which were calibrated before each session. <sup>17</sup> Horizontal head impulses (amplitude: 20-30°; duration: 150–200 ms; peak velocity: about 300 °/s; peak acceleration: about 10,000 °/s<sup>2</sup>) were applied by an investigator standing behind the subject who was visually fixing upon a target light 1.24 m straight ahead. The directions of the head impulses were pseudorandomly intermingled and four to six impulses were performed in each direction. The gain of the horizontal semicircular-ocular reflex was determined by computing the coefficient eye-in-head displacement divided by head-in-space displacement as head-in-space moved from 3° to 7° eccentricity from straight ahead. <sup>18</sup>



As the representative gain during head impulses to either side, the median value was computed. Median gain values were considered pathologic, if they were below two standard deviations of the average gain determined in healthy controls. This healthy control group consisted of 12 healthy subjects (six women;  $43 \pm 10$  y), selected by age frequency matching from a previously published population of 28 healthy subjects (15 women; 18 – 75 y,  $44 \pm 15$  y).<sup>19</sup>

All patients were investigated by routine pure tone audiometry to ascertain the absence of conductive hearing loss. Hearing was normal in nine patients, while sensorineural hearing loss comprising the mid ( $> 0.5 \text{ kHz} \leq 2 \text{ kHz}$ ) to high ( $> 2 \text{ kHz} \leq 8 \text{ kHz}$ ) frequency range was present in the remaining six patients (frequency range definition according to Stephens (2001)<sup>20</sup>). The sensorineural hearing loss affected both ears symmetrically in five patients and was accentuated on the right ear in one patient.

**Statistical analysis.** Statistical analysis was performed using MATLAB (The Mathworks, Natick, MA), version 7.5. Unpaired two-tailed t-test was used for average analysis and the Wilcoxon rank-sum test was used for CMT sub-classification analyses. Principal component analysis (PCA) was used for correlation analyses between vestibular and peripheral nerve conduction parameters, as PCA is more appropriate than standard linear regression analysis for dependent, i.e. inter-correlated variables.<sup>21</sup> For correlation analyses with age (independent variable) and vestibular and nerve conduction data, respectively, robust linear regression analysis (robustfit.m) was used. A level of significance of 0.05 was adopted and 95% confidence intervals (CI) calculated.

## RESULTS

At the time of the study the median age of patients (N = 15; eight women) was 48 ( $\pm$  17) years (range 23-74 y). Abnormal clinical findings included: 1) unilateral (N = 5) or bilateral (N = 2) abnormal bedside head-impulse test; 2) stand and gait ataxia (N = 11); 3) sensory deficits (touch: N = 6; pain: N = 3; temperature: N = 3; position: N = 6; vibration: N = 8), muscle atrophy (N = 12), muscle weakness (N = 13), weak or absent tendon reflexes (N = 13), and pes cavus (N = 5).

Charcot-Marie-Tooth (CMT) phenotypes included: CMT1, CMTX, CMT2, CMT4, and intermediate (DI) CMT (details summarized in Table 1). Five patients could not be classified. The genotype included duplication in the peripheral myelin protein 22 gene (PMP22), mutation in the gap junction B1 gene (GJB1, Connexin 32), and point mutation in the myelin protein zero gene (MPZ). Six patients (one patient with CMT2, one patient with CMT4, 4 patients with unclassified CMT) remained genetically undefined, whereby mutations in the PMP22, GJB1, MPZ, and mitofusin 2 genes were excluded. Family history was positive in all six patients. Genetic testing was not performed in one patient (patient ID 15 in Table 1), but family history was positive for Charcot-Marie-Tooth Type 1A.

On the basis of nerve-conduction studies and the genotype patients were classified into a primary demyelinating (N = 13) or a primary axonal group (N = 2, patient ID 5 and ID 10 in Table 1). Average age between demyelinating ( $47 \pm 13$  y) and axonal ( $46 \pm 15$  y) patients were not different (unpaired two-tailed t-test:  $p > 0.8$ ).

Cervical vestibular-evoked myogenic potentials (cVEMP) were registered in 14 patients. Due to a technical defect, one patient was not tested by cVEMP. In 11 patients, cVEMP were detectable from both sternocleidomastoid muscles (SCM), in one patient

(patient ID 9) from one SCM side only, and in two patients (patient ID 6 and ID 4) cVEMP were bilaterally absent. For further comparison, the 74 year old patient (ID 4) with bilaterally absent responses was excluded since cVEMP can be absent also in healthy subjects over age 60 <sup>22</sup>. The remaining 13 patients included in further analysis were all aged < 60 years (see Fig. 2B).

Figure 1 shows examples of cVEMP traces (averaged over 200 repetitions) recorded from the left (A) and right (B) SCM in one healthy subject (black line) and one patient (dashed grey line). In the patient (patient ID 13), uncorrected averaged raw peak-to-peak amplitudes were within the normal range of healthy subjects while p13- and n23-latencies were prolonged in responses to clicks delivered on the left ear (dashed vertical lines depict upper limit of normal p13 and n23 latencies; for values see Methods).

Averaged uncorrected raw peak-to-peak amplitudes ( $\pm 1$  SD) in all patients (i.e. 26 ears) were  $91 \pm 101$   $\mu$ V (Fig. 2A). Average asymmetry ratio ( $\pm 1$  SD) of uncorrected amplitudes was  $35 \pm 26$  % (Fig. 2B). Although average asymmetry ratio resulted within the normal range ( $37 \pm 26$  %; unpaired two-tailed t-test  $p > 0.2$ ; cutoff of upper normal limit set to 46 % according to Wegampola and Colebatch <sup>16</sup>), six of 13 patients showed abnormal values. Values ranged between 47 to 100 % ( $63 \pm 17$  %; unpaired two-tailed t-test  $p < 0.001$ ) in five patients and were bilaterally absent in patient ID 6 (see \* in Fig 2B). cVEMP latencies were abnormal in nine patients. p13 latencies (Fig. 2C) were prolonged in five patients (unpaired two-tailed t-test  $p = 0.01$ ), in one patient on both sides ( $23.1 \pm 0.6$  ms), in one patient on the right side (21.7 ms), and in three patients on the left side only ( $21.8 \pm 0.4$  ms). n23 latencies (Fig. 2D) were prolonged in nine patients (unpaired two-tailed t-test  $p = 0.01$ ): in six patients unilaterally ( $28.9 \pm 0.7$  ms; three right-sided and three left-sided) and in three patients bilaterally ( $29.8 \pm 1.2$  ms). Only in one patient (patient ID 11), both, p13 ( $23.1 \pm 0.5$  ms) and n23 ( $30.4 \pm 1.3$  ms)

latencies were prolonged in both ears. CMT sub-group analyses showed no differences for cVEMP asymmetry ratios, p13, and n23 latencies (Kruskal-Wallis:  $p > 0.2$ ). Neither were differences found between predominant demyelinating ( $N = 10$ ; asymmetry ratio:  $35 \pm 30 \%$ ; p13:  $19 \pm 2$  ms; n23:  $27 \pm 2$  ms) and predominant axonal neuropathies ( $N = 2$ ; asymmetry ratio:  $50 \pm 5 \%$ ; p13:  $18 \pm 0.6$  ms; n23:  $27 \pm 0.9$  ms; unpaired two-tailed t-test:  $p > 0.1$ ). We emphasize, however, that sub-group analyses must be evaluated with caution because of the small number of patients participating in this study.

Compared to healthy subjects, the average gain of the high-acceleration horizontal vestibulo-ocular reflex, as determined by the quantitative head impulse test (qHIT), was reduced in patients with CMT (Fig. 3; average gain  $\pm 1$  SD of pooled ears from healthy subjects:  $0.86 \pm 0.07$ ; pooled ears from patients:  $0.67 \pm 0.24$ ; paired t-test  $p < 0.001$ ; symbols as in Fig. 2). Overall, nine of 15 patients showed deficient gain values in one (CMT1A,  $N = 1$ ; CMTX,  $N = 1$ ; undefined CMT,  $N = 2$ ) or both directions (CMT1A,  $N = 1$ ; CMT2,  $N = 1$ ; DI-CMT,  $N = 1$ ; undefined CMT,  $N = 2$ ), while gain values to both sides were normal in six patients. As for cVEMP, average gain values during qHIT to either side were not different among CMT sub-groups (Kruskal-Wallis:  $p > 0.1$ ) and between primary demyelinating ( $0.67 \pm 0.2$ ) and primary axonal neuropathies ( $0.67 \pm 0.04$ ; unpaired two-tailed t-test:  $p > 0.1$ ). Again, we emphasize that due to the small number of patients in the respective subgroups, this finding can only be preliminary.

In summary, we found that vestibular function was impaired in the majority, i.e. in 14 of 15, of our patients with CMT disease. In 8 of 13 patients (for comparison of otolith and semicircular canal function only patients with both, elicitable cVEMP and qHIT, were taken) both, otolith and semicircular canal function were impaired and the side of otolith and semicircular canal impairment (i.e. the affected ear) correlated in 6 patients. Interestingly, ‘isolated’ otolith impairment, as determined by increased asymmetry ratio

and / or prolonged p13-n23 cVEMP latencies, occurred more frequently (4/13 patients) than ‘isolated’ semicircular canal deficiency (1 /13 patients), as assessed by qHIT. Moreover, all patients with semicircular canal impairment also evidenced otolith abnormalities, while the reverse was not true.

Vestibular function was further compared with peripheral nerve conduction parameters (see Table 1). Regression analyses demonstrated moderate correlation between cVEMP p13 latencies and median nerve conduction velocities (principal component analysis;  $R^2=0.17$ , slope=-4.0, 95% CI=-47.3 to -2.1), between cVEMP p13 latencies and peroneal nerve distal motor latencies (principal component analysis;  $R^2=0.28$ , slope=1.7, 95% CI=1.3 to 9.2), and between cVEMP amplitudes and ulnar nerve distal motor latencies (principal component analysis;  $R^2=0.3$ , slope=0.02, 95% CI=0.02 to 0.05). All other correlation analyses between vestibular and peripheral neuropathy data as well as correlation analyses (regression analysis) between age and electrophysiological data resulted non-significant. Thus, although the first two findings point towards a positive link between the degree of vestibular impairment and peripheral neuropathy deficiency, results, in particular also considering the moderate significance and the inverse correlation between cVEMP amplitudes and ulnar nerve distal motor latencies, should be interpreted with caution due to the small patient sample size.

## DISCUSSION

This study demonstrates the high prevalence of coexisting vestibular and peripheral neuropathy in a group of patients affected by Charcot-Marie Tooth disease (CMT). Vestibular impairment was present in the majority of CMT patients, irrespective of their clinical phenotype and their genotype. Interestingly, cervical vestibular-evoked myogenic potentials (cVEMP) were more frequently impaired than the quantitative head impulse test (qHIT) suggesting that the former might have a higher sensitivity in detecting vestibular, specifically otolith, impairment than the latter.

Our results are in line with previous findings in a more heterogeneous population of patients with polyneuropathy, where we recently identified that postural imbalance was a multisensory balance disorder due to a concomitant vestibular and proprioceptive impairment, rather than due to an isolated proprioceptive sensory loss.<sup>3</sup>

Characterizing patients with vertigo and / or dizziness requires information concerning the function of the vestibular end-organs as a whole. While it is known from single case reports that semicircular canal function can be involved in inherited neuropathies,<sup>6, 7</sup> to our best knowledge, this is the first study characterizing otolith function. cVEMP were investigated in this study, as vestibulo-spinal pathways are important structures when evaluating balance control.

Air conducted sound stimuli used to induce cVEMP activate vestibular afferent neurons predominantly originating from the saccular macula that project via vestibulo-spinal pathways to the neck muscles, specifically to the motor neurons of the ipsilateral sternocleidomastoid muscle. A lesion anywhere in these pathways can result in abnormal cVEMP. In our study we found that cVEMP latency was affected more often than cVEMP amplitude. This pattern is in analogy with other pathologies affecting

primary the vestibular nerve or central vestibular pathways, such as multiple sclerosis, vestibular schwannoma, and inferior vestibular neuritis,<sup>23, 24</sup> and explained by a reduction in conduction velocity along the nerve fibers.<sup>25</sup> In fact, the majority of our patients had demyelinating neuropathy, which results in slow nerve-conduction velocities. In contrast, other primary vestibular end-organ disorders, e.g. Menière's disease,<sup>26</sup> predominantly evidence reduced cVEMP amplitudes while latencies are relatively preserved (see Wegampola et al. (2005) for review<sup>15</sup>).

When comparing results from cVEMP to qHIT, our study suggests that cVEMP may be more sensitive for detecting vestibular involvement in CMT patients. In fact, beside the higher proportion of cVEMP compared to qHIT abnormalities found in our patients, we also observed that reduced qHIT was always associated with cVEMP abnormalities while the reverse was not true. That patients' average qHIT differed from healthy controls while it did not for cVEMP parameters, furthermore, indicates that cVEMP may be particularly useful for detecting early stages of vestibular impairment. Presumably, differences between cVEMP and qHIT sensitivity rise from prolonged latencies appearing earlier due to the polysynaptic pathway activation in cVEMP versus to the oligosynaptic pathways stimulated by qHIT.

The small number of patients and the heterogeneous phenotype are of course limitations of this study and comparison of vestibular function among different CMT genotypes was not reliably possible. The high percentage of vestibular impairment found in our small cohort, nevertheless, emphasizes the importance of routinely investigating vestibular function in CMT patients, ideally by cVEMP. Fortunately, technical advancements within the last few years have made laboratory HIT<sup>27</sup> and cVEMP<sup>28</sup> assessment easily accessible and have paved the way for exploring its clinical applicability, in particular with regards to patients symptoms, which, to date, still

remains a major unresolved issue.<sup>29</sup> However, recognizing a combination of vestibular impairment and peripheral neuropathy is in fact highly relevant since physical therapy should then focus on vestibular exercises, which have been shown to enhance vestibular function and improve compensatory sensory strategies, in particular, vision.<sup>30</sup>



## FIGURES

**Figure 1.** Examples of cVEMP responses

**Legend:** Examples of cVEMP responses recorded from the left (left panel) and right (right panel) sternocleidomastoid muscles (SCM) in one healthy subject (black line) and in one patient (dashed grey line). Traces consist of averaged (200 repetitions) unrectified electromyogram signals from each SCM. Note the prolonged p13n23 peak latencies evoked by air-conducted sound stimuli delivered in the patients left ear via headphones (left panel). Peak-to-peak p13n23 amplitudes, in contrast, are similar for the patient and healthy subject. Dashed vertical lines: upper limit of normal p13 and n23 latencies.

**Figure 2.** cVEMP uncorrected average amplitudes, asymmetry ratio, p13 and n23 latencies of individual patients

**Legend:** cVEMP uncorrected average amplitudes of individual patients (A), asymmetry ratio (B), p13 (C) and n23 (D) latencies of individual patients. (A) cVEMP amplitudes to air-conducted sound stimuli delivered to both ears in individual patients are connected by dashed lines. Circles on the left and right: ears with higher and lower amplitude responses, respectively. Filled square: mean  $\pm$  1SD of healthy controls. (B) Side to side differences of uncorrected cVEMP amplitudes expressed as asymmetry ratio plotted against patients' age. Symbols depict CMT phenotypes:  $\square$ : patients classified as CMT1A,  $\diamond$ : as CMT2, +: as CMTX, x: as DI- CMT, \*: as undefined CMT.  $\bullet$ : patients' mean asymmetry ratio ( $\pm$  1 SD) plotted against the subjects' mean age . Note that in the single patient with CMT4D no cVEMPS could be elicited bilaterally, therefore this subgroup is not shown. Horizontal dashed line: upper normal limit for healthy subjects (average + 2 SD). (C, D) p13 and n23 latencies for pooled ears from individual patients. Symbols of subgroups as in subpanel B.  $\bullet$ : mean and 95% confidence interval of all

patients. Horizontal dashed lines: upper and lower latency limits (average  $\pm$  2 SD) of healthy subjects.

**Figure 3.** Gains of the horizontal vestibulo-ocular reflex during head impulses to both sides in patients and healthy controls

**Legend:** Gains of the horizontal vestibulo-ocular reflex during head impulses to both sides in patients and healthy controls. Mean and 95% confidence interval over all healthy subjects (filled square on the left), all patients (filled circle on the right) and of patients' subgroups (symbols as in Figure 2) are depicted. Horizontal dashed line: lower gain limits of healthy subjects (average - 2 SD).

**Table 1.** Phenotype, genotype and electrophysiological results of patients with Charcot-Marie-Tooth disease

Patient ID/ Age/ Sex/	Phenotype	Genotype	Median nerve		Ulnar nerve		Peroneal nerve	
			MNCV (45-52)*	DL (<3.5-4)*	MNCV (41-45)*	DL (<3.1-3.5) *	MNCV (37-44)*	DL (<5-.9)*
1/47/F	CMT1A	PMP22 dupl.	34	14.3	32	7.8	27.	4.5
2/61/M	CMT1A	PMP22 dupl.	n.p.	n.p.	13	8.5	11	11.2
3/56/F	CMT1A	PMP22 dupl.	26	9	32	7.4	28	10.3
4/74/F	CMT1A	PMP22 dupl.	n.p.	n.p.	16	11.3	12	16.4
5/57/M	CMT2	undefined	41	6.2	42	7.7	0	0
6/50/F	CMT4D	undefined	27	11	31.5	8.6	n.p.	n.p.
7/35/F	CMTX1	GJB1/Cx32	41	3.9	43.5	3	36	5.1
8/49/M	CMTX1	GJB1/Cx32	34	5.4	41	3.5	19	3.9
9/23/M	CMTX1	GJB1/Cx32	28	8.5	n.p.	n.p.	n.p.	n.p.
10/43/F	DI-CMT	MPZ	30	5.6	43	3.4	31	5.7
11/44/M	CMT	undefined	28	6.8	31	5.4	12	13.5
12/53/M	CMT	undefined	34	7.3	41	5.2	25	7.9
13/47/F	CMT	undefined	37	4.9	45	4.6	30	6.7
14/25/M	CMT	undefined	41	5.2	38	5.4	33	4.1
15/23/F	CMT	n.p.	16	8	n.p.	n.p.	25	11

Legend: F = female; M = male; MNCV= motor nerve conduction velocity (m/s); DL= distal motor latency (ms); \*: normal values of MNCV and DL; n.p. = not performed; CMT=Charcot-Marie-Tooth disease; CMT1=autosomal-dominant demyelinating CMT; CMT2=autosomal-dominant or autosomal-recessive axonal CMT; DI-CMT=intermediate CMT; CMT4=autosomal-recessive demyelinating CMT; CMTX=X-linked CMT; GJB1/Cx32=gap junction B1/connexin 32; PMP22 dupl.=peripheral myelin protein 22 duplication; MPZ=myelin protein zero. Normal values reported in parenthesis.

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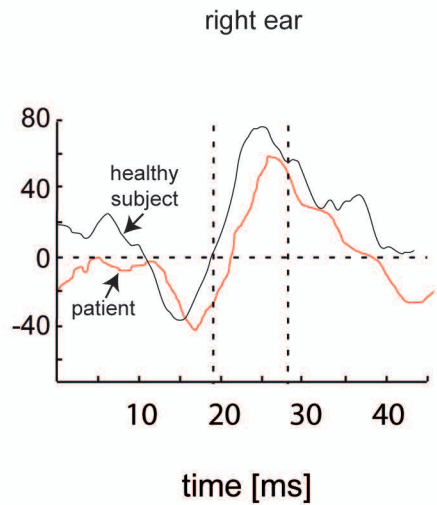
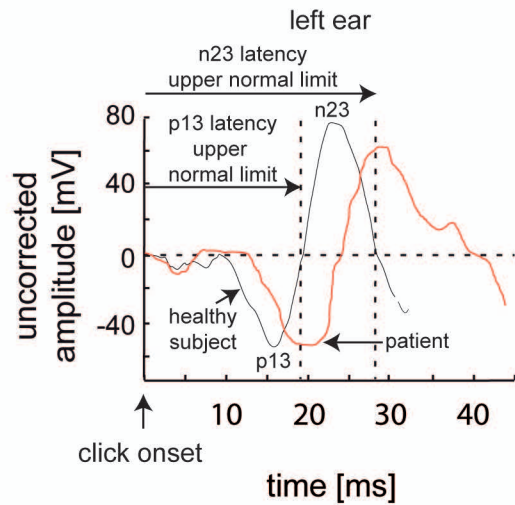


Fig. 1

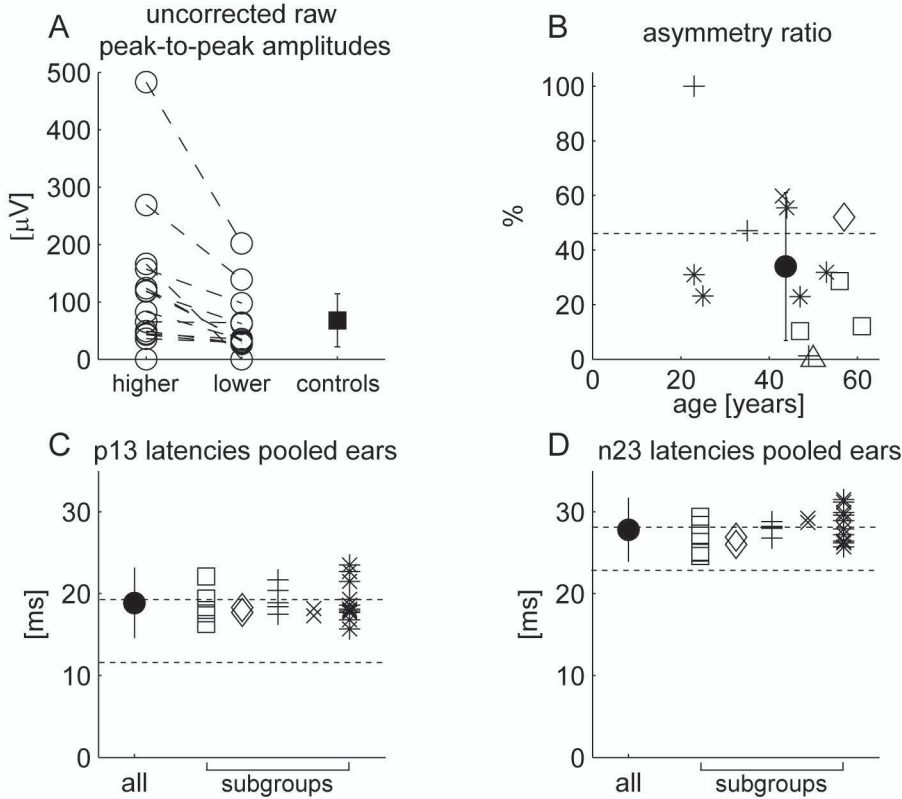


Fig. 2

**Figure 2.** cVEMP uncorrected average amplitudes, asymmetry ratio, p13 and n23 latencies of individual patients

**Legend:** cVEMP uncorrected average amplitudes of individual patients (A), asymmetry ratio (B), p13 (C) and n23 (D) latencies of individual patients.

(A) cVEMP amplitudes to air-conducted sound stimuli delivered to both ears in individual patients are connected by dashed lines. Circles on the left and right: ears with higher and lower amplitude responses, respectively. Filled square: mean  $\pm$  1SD of healthy controls.

(B) Side to side differences of uncorrected cVEMP amplitudes expressed as asymmetry ratio plotted against patients' age. Symbols depict CMT phenotypes:  $\square$ : patients classified as CMT1A,  $\diamond$ : as CMT2,  $+$ : as CMTX,  $\times$ : as DI-CMT,  $*$ : as undefined CMT.  $\bullet$ : patients' mean and 95% confidence interval. Note that in the single patient with CMT4D no cVEMPS could be elicited bilaterally, therefore this subgroup is not shown. Horizontal dashed line: upper normal limit for healthy subjects (average + 2 SD).

(C, D) p13 and n23 latencies for pooled ears from individual patients. Symbols as in subpanel B.  $\bullet$ : mean and 95% confidence interval of patients pooled ears. Horizontal dashed lines: upper and lower latency limits (average  $\pm$  2 SD) of healthy subjects.



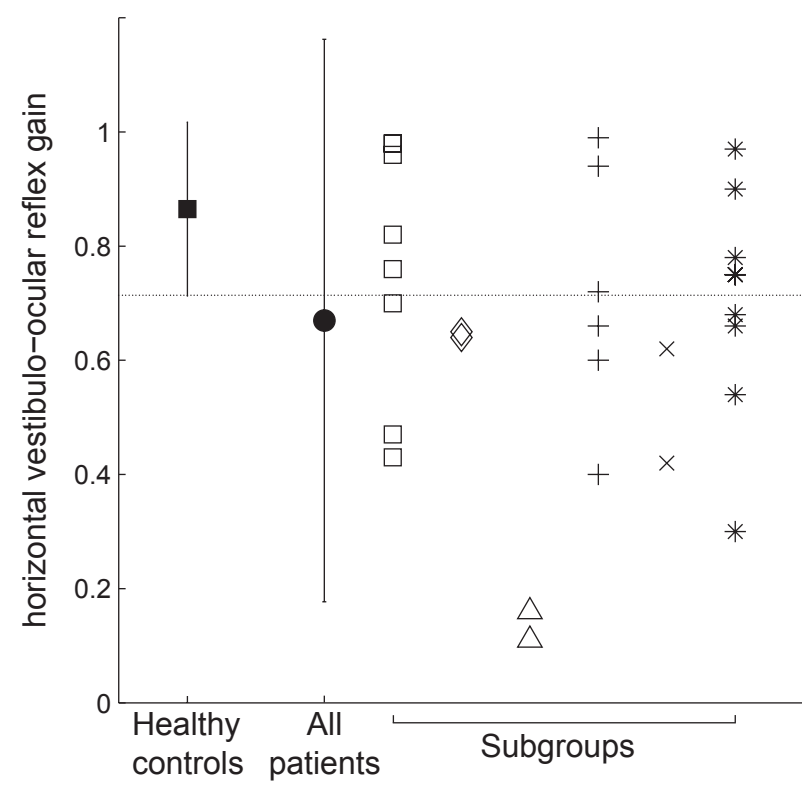


Figure 3